Epigenetics in cancer stem cell initiation and clinical outcome prediction

Grant Award Details

Epigenetics in cancer stem cell initiation and clinical outcome prediction

Grant Type: New Faculty I

Grant Number: RN1-00550

Project Objective: The overall goal of this grant is to identify and characterize the molecular pathways that regulate global levels of histone modifications in cancer and other cells and to translate cancer epigenetic patterns into diagnostic and prognostic tests.

Investigator:

Name:	Siavash Kurdistani
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Cancer, Solid Tumors

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $3,063,450

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Epigenetics in cancer stem cell initiation and clinical outcome prediction

Public Abstract: Cancer is responsible for approximately 25% of all deaths in the US and other developed countries. For women, breast and lung cancers and for men, cancers of prostate and lung are the most prevalent and the most common cause of deaths from cancer. While a large number of treatment modalities such as surgery, chemotherapy, radiation therapy, etc. have been developed, we still are far from finding a cure for most cancers. So, more research is needed to understand the basic processes that are subverted by cancer cells to gain a proliferative advantage. In addition, cancer patients show a great deal of heterogeneity in the course and outcome of the disease. Therefore it is important to be able to predict the clinical outcome of the patients so that appropriate therapies can be administered. Clinical outcome prediction is based generally on tumor burden and degree of spread with additional information provided by histological type and patient demographics. However, patients with similar tumor characteristics still show heterogeneity in the course and outcome of disease. Thus, accurate sub-classification of patients with similar clinical outcomes is required for development of more efficacious therapies.

One important molecular process that is altered in cancer is the epigenetic regulation of gene expression. In humans, DNA is tightly wrapped around a core of proteins called histones to form chromatin—the physiologically relevant form of the genome. The histones can be modified by small chemical molecules which can affect the structure of chromatin, allowing for a level of control on gene expression. The patterns of occurrences of the histone modifications throughout chromatin are highly regulated and affect all molecular processes that are based on DNA. This information which is heritable but not encoded in the sequence of DNA is referred to as 'epigenetics.'

A challenge in biology is to understand how histone modifications which can number to more than 150, contribute to normal gene regulation and how their alterations contribute to development of cancer stem cells. These cells are thought to be responsible for maintain the bulk of the tumor and need to be completely eradicated if we were to cure a given cancer. By studying primary cancer tissues and viruses that cause tumor, we have found that one histone modification plays a critical role in transforming a normal call to a tumor cell, potentially generating a cancer stem cell. We have found that he same histone modifications can be used as a biomarker to predict clinical outcome of patients. We now propose to study this process in more depth, discover other important histone modifications that contribute to cancer development and progression and use this knowledge to develop standard, simple and robust assays for predicting clinical outcome of cancer patients. Our work may also lead to identification important molecules that can be targeted for cancer therapy.

Statement of Benefit to California:	Cancer is a devastating disease that is becoming more prevalent as the population ages. While scientists have developed a general framework of how cancer initiates, there remains significant gaps in our knowledge about how cancer arises from a normal cell. One difficulty with studying cancer is the heterogeneity in the types of cells that exist within a given cancer tissue. Some of these cells have recently been shown to have stem cell-like properties and when isolated can reestablish the original tumor. These 'cancer stem cells' are thought to be responsible for maintaining the bulk of the tumor and need to be completely eradicated if we were to cure a given cancer. There is also a great deal of differences in the course and outcome of cancers with seemingly similar attributes, making application of appropriate therapies difficult. Our proposal aims to understand some of the basic processes that may contribute to development of cancer stem cells and to use this knowledge to develop proper clinical tests for prediction of cancer patients' clinical outcome. This would be beneficial for people of California as it may lead to personalization of cancer therapy. Our work may also lead to identification of critical molecules that need to be therapeutically targeted to improve rates of cancer therapy. Identification of such molecules may lead to innovative discoveries and patents that may be exploited by the biotech industry in California, and thereby improve the economy of California as well.

Source URL: https://www.cirm.ca.gov/our-progress/awards/epigenetics-cancer-stem-cell-initiation-and-clinical-outcome-prediction